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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,014	06/06/2006	Shuchong Pan	07039-409US1	9426

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EXAMINER	
WANG, CHANG YU	
ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
10/12/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/561,014	PAN ET AL.	
	Examiner	Art Unit	
	CHANG-YU WANG	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,6,8,10,16 and 45-48* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,6,8,16,45,46 and 48* is/are rejected.

8)☒ Claim(s) *10 and 47* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/11/11, 5/10/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/21/10 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendment filed 12/21/10 is acknowledged. Claims 2-5, 7, 9, 11-15, and 17-44 are cancelled. Claims 1, 6, 16 and 45 are amended. Claim 48 is newly added. Claims 1, 6, 8, 10, 16, 45-47 and new claim 48 are pending in this application and are under examination with respect to SEQ ID NOs: 1, 3 and 36 in this office action.

3. Applicant's arguments filed on 12/21/10 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

4. The objection to claims 45 and 46 is withdrawn in response to Applicant's amendment to the claims.

The rejection of claims 1, 6, 16 and 45 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement due to new matter is withdrawn in response to Applicant's amendment to the claims.

Claim Rejections/Objections Maintained

In view of the amendment filed on 12/21/10, the following rejections are maintained.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 8, 16, 45-46 and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for a purified polypeptide BNP2 comprising the amino acid sequence of SEQ ID NO: 3 and 36, does not reasonably provide enablement for a structurally and functionally undefined polypeptide comprising an amino acid sequence having at least 90% to 95% identity to the amino acid sequence of SEQ ID NO:1 as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in the scope with these claims. The rejection is maintained for the reasons made of record and the reasons set forth below.

Claims 1, 6, 8, 16, 45-46 and 48 as amended are directed to a purified mature BNP2 polypeptide comprising an amino acid sequence having at least 90% or 95%

identity to the amino acid sequence of SEQ ID NO:1 and a pharmaceutical composition comprising the claimed polypeptides.

Briefly, claims 1, 6, 8, 16, 45-46 and 48 are rejected because the specification fails to teach what the function and activity of SEQ ID NO:1 are. Although SEQ ID NO:1 is part of SEQ ID NO:3, the specification fails to teach how to make and use the peptide of SEQ ID NO:1. The polypeptides comprising structurally and functionally undefined sequences derived from SEQ ID NO:1 are not enabling because the function and activity of SEQ ID NO:1 and their variants are unknown.

On p.5-6 of the response, Applicant argues that instant claims are fully enabled because the amino acid sequence of SEQ ID NO:1 is a 33-amino acid polypeptide present at the C-terminus of human BNP2. Applicant further argues that the RNA encoding the polypeptide of SEQ ID NO:1 and the protein can be detected in heart tissue from heart failure patients in examples 1 and 5. Applicant argues that the specification also teaches a variety of other species having 90% or 95% identity to SEQ ID NO:1 at paragraph [0030] and thus a skilled artisan would know how to make and use the claimed polypeptides without undue experimentation. Applicant's arguments have been fully considered but they are persuasive.

Contrary to Applicant's arguments, the specification only discloses that an up-regulated expression level of SEQ ID NO:3 or 36 is found in heart tissue from heart failure patients. The specification fails to provide sufficient guidance as to how all the polypeptides comprising fragments and variants with at least 90% or 95% identity to the

amino acid sequence of SEQ ID NO:1 as in instant claims are related to the amino acid sequence of SEQ ID NO:3 or 36. The specification does not show that the claimed variant polypeptides comprising an amino acid sequence having at least 90% or 95% identity to the amino acid sequence of SEQ ID NO:1 are also up-regulated and thus would be associated to the same disease or other diseases as in SEQ ID NO:3 or 36. The specification also fails to show that whether the claimed variant polypeptides comprising an amino acid sequence having at least 91% or 97 identity to SEQ ID NO:1 would act in the same manner as SEQ ID NO:3 and 36 in the patients suffering from heart failure and thus can have the same utility as SEQ ID NO:3 and 36.

As previously made of record, the events of transcription and translation of each gene are independent from each other. The specification fails to show that the transcription and translation of the claimed polypeptides and variants comprising an amino acid sequence at least 90% or 95% identity to SEQ ID NO:1 are positively associated with SEQ ID NO:3 and 36 and thus can also be used as an diagnostic marker of heart failure. Thus, it is unpredictable whether all the claimed variant polypeptides comprising an amino acid sequence having at least 90%-95 identity to SEQ ID NO:1 are useful for a diagnostic marker of any diseases or other purposes since there is no guidance to indicate how the variant polypeptides are related to SEQ ID NO:3 or 36. It is also unpredictable which, if any other variant polypeptides would be similarly up-regulated, since the regulation of a gene or a protein is not dependent on the sequence of the protein. Since the specification fails to provide sufficient guidance as to whether the variant polypeptides would be up-regulated and whether they are

related to heart diseases or other diseases, a skilled artisan cannot contemplate how to use the claimed variant polypeptides. Thus, a skilled artisan cannot contemplate how to use the claimed genus of variant polypeptides except SEQ ID NO:3 and 36.

Note that the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, it is unpredictable what changes can be made and still maintain activity; it is also unpredictable whether the claimed undefined polypeptide variants can have the same utility as SEQ ID NO:3 or 36 as a diagnostic marker; and thus the experimentation left to those skilled in the art is extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation. Note that

"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)" See MPEP § 2164.03.

Accordingly, the rejection of claims 1, 6, 8, 16, 45-46 and 48 under 35 U.S.C. 112, first paragraph, because the specification does not enable the invention commensurate in scope with the claims is maintained.

Claim Rejections - 35 USC § 112

6. Claims 1, 6, 8, 16, 45-46 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 6, 8, 16, 45-46 and 48 as amended are directed to a purified mature BNP2 polypeptide comprising an amino acid sequence having at least 90% or 95% identity to the amino acid sequence of SEQ ID NO:1 and a pharmaceutical composition comprising the claimed polypeptides.

The claims encompass a genus of polypeptides comprising structurally and functionally undefined variants having at least 90% or 95% identity to a fragment of SEQ ID NO:1. Applicant has not disclosed sufficient species for the broad genus of variant polypeptides or fragments related to SEQ ID NOs:1, 3 and 36. The claims do not require any particular biological activity/conserved structure/distinguishing feature. Thus, the claims encompass a genus of polypeptides that is defined only by sequence similarity. However, the instant specification fails to provide information to demonstrate Applicant's possession the entire genus of the polypeptide variants and fragments that are encompassed by these claims.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant is in possession of and what Applicant is claiming. From the specification, it is clear that Applicant is in possession of SEQ ID NOs: 3 and 36, which have a known function and activity. However, the claims are not only drawn to polypeptides having the above sequences but also to variants and fragments and

polypeptides derived from SEQ ID NOs:1, 3 and 36 and variants and fragments comprising sequences having at least 90% or 95% identity to the amino acid sequence of SEQ ID NO:1. The claims only require the polypeptides to share some degree of structural similarity to SEQ ID NOs:1, 3 and 36. The specification only describes SEQ ID NOs: 3 and 36 and fails to teach the function of SEQ ID NO:1 or describe any other related proteins with limited homology. In this case, the only factor present in the claim is a partial structure in the form of a recitation of sequence similarity or percent identity. There is not even identification of any particular portion of the structure that must be conserved. The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of variant and fragment polypeptides. While a generic sequence is provided, there is merely a set of common properties: there is no description of the conserved regions which are critical to the function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the variant and fragment polypeptides in the genus from other polypeptides are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the variant and fragment polypeptides encompassed: there is no guidance in the art as to what the defining characteristics of an isolated polypeptide with limited homology to SEQ ID NOs: 3 and 36 might be. Since the common characteristics/features of the isolated variant and fragment polypeptides are unknown, a skilled artisan can not envision the functional correlations

of the genus with the claimed invention. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the genus of proteins.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the claimed polypeptide and composition have not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-*

Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement. See MPEP 2163.

Conclusion

Allowable Subject Matter

7. Claims 10 and 47 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

On p. 7 of the response, Applicant argues that in light of the amendment and the remark, claims 10 and 47 are allowable. Contrary to Applicant's arguments, claims 10 and 47 are still objected to because claims 1 and 16 are still rejected (see the rejection set forth above).

8. Claims 1, 6, 8, 16, 45-46 and 48 are rejected.

9. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should

applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chang-Yu Wang
September 28, 2011

/Chang-Yu Wang/
Primary Examiner, Art Unit 1649